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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/412,947 | 10/05/1999 | SUDHIR AGRAWAL | HYZ-050CP2 | 1312 |

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|---|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 06/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/412,947 | Applicant(s) AGRAWAL, SUDHIR |
|---|---|---|
| | Examiner Janet Epps | Art Unit 1635 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 March 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20 and 23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

## DETAILED ACTION

### *Continued Prosecution Application*

1. The request filed on 3-18-2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/412,947 is acceptable and a CPA has been established. An action on the CPA follows.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Response to Amendment*

3. The amendment filed 3-22-02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicants have amended the paragraph on page 58, lines 25-59. However, Applicant's amendment does not appear to be supported by the specification as originally filed. According to Applicants, amending the specification on page 58, at line 30, by changing the term "inverted chimeric" to "antisense" is an obvious error, however it is not immediately apparent why this change is obvious, since Applicants also changed the reference sequence to recite Oligo 164 instead of Oligo 190. Furthermore, changing line 29 to recite Oligo 165 instead of Oligo 164, also does not appear as an obvious error in the specification as originally filed since both oligos appear to have the same overall effect on tumor size as set forth in Figure 1.

Applicant is required to cancel the new matter in the reply to this Office Action.

***Response to Arguments***

4. Claims 1-20 and 23- 33 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting proliferation of cancer cells *in vitro*, and in an mouse model comprising the administration of HYB 165, does not reasonably provide enablement for treatment of cancer in a patient *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in the Official Action mailed 10-24-2000.

Applicant's arguments filed10-17-2001 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that, in light of the teachings of Milner et al., which teach a combinatorial technique that allows simultaneous assessment of all possible ONs within a given region identifying sequences open to duplex formation, one of ordinary skill in the art would know how to determine effective antisense oligonucleotides without undue experimentation. Additionally, Applicants reference Monia et al., Agrawal et al., Craig et al., Galderisi et al., and Applicant's own Examples 27-29 as support for their assertion that HYB 165 (SEQ ID NO: 4) and other oligonucleotide sequences were shown to be operable *in vivo*. Additionally, Applicants submit that (1) at least one oligonucleotide works *in vivo* (and in fact more than one oligonucleotide has been shown to work *in vivo*); (2) because there is a correlation between *in vitro* and *in vivo* results, there is a reasonable expectation that antisense oligonucleotides shown to work *in vitro* would also be expected to work *in vivo;* (3) it would not require undue experimentation to find other oligonucleotides that would be functional besides HYB 165; and (*paraphrasing*) (4) claims only cover operable embodiments. Therefore,

applicants concluded that antisense art is no longer unpredictable, and the specification enables the scope of the claimed invention.

However, contrary to Applicant's assertions, it is first noted that although combinatorial arrays may potentially be useful for obtaining valuable information, as described by Milner et al., their use is not an industry standard since many experts worry that gene arrays may generate too much misleading data (see McGowan, 2002). In regards to the correlation between identifying effective antisense compounds *in vitro* using the teachings of Milner et al., and the production of actual *in vivo* antisense effects, contrary to the teachings of Milner et al. (1997), Crooke (1998) states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies *[references omitted]*."

In regards to the *in vivo* antisense effects described in Monia et al., Agrawal et al., Craig et al., and Galderisi et al., the results set forth in these references are not sufficient to conclude that antisense therapeutics in general are unpredictable, since the results obtained in these references were achieved with antisense compounds that are distinct from those compounds encompassed by the methods of the instant invention. Applicants have not provided any correlative evidence that the experimental results obtained by using chemically and structurally distinct compounds are generally predictive of the behavior of all antisense compounds, having a distinct sequence composition, length, chemical modification, and mRNA target.

Additionally, in response to Applicant's assertion that Examples 27-29 provide sufficient evidence that the claimed invention is fully enabled vivo, Applicants have not provided a clear nexus between the *in vivo* results obtained using the mouse model set forth in Example 28 of the specification, and inhibiting the proliferation of cancer cells in all organisms. Example 28, describes results obtained using the HYB 165 oligonucleotide, however claim 1 is not limited to the oligonucleotide according to HYB 165 (SEQ ID NO:4). Additionally, it is noted that the behavior of antisense compounds are unpredictable within different cellular environments. As stated in the previous Office Action, Crooke (1998) describes a variety of factors which influence cellular uptake and distribution of antisense base therapeutics, which include: length of the oligonucleotide, modifications, sequence of oligonucleotide and cell type. Due to the unpredictability in cellular behavior associated with variations in sequence, length, and modifications of the oligonucleotides encompassed by the present invention, it is likely that the examples comprising the use of the HYB 165 oligonucleotide are not representative of all oligonucleotides encompassed by the claimed invention. Applicants have not addressed the various factors that contribute to the unpredictable behavior of antisense compounds in different cellular environments, as described by Crooke (1998).

Applicants further argue that the phrase, "consists essentially of the nucleotide sequence set forth in SEQ ID NO:4," is clear because the language appears in the claims of US 5,969,117, and since it indicates that the nucleotide sequence is that sequence set forth in SEQ ID NO: 4. However, contrary to Applicant's assertions, the phrase "consists essentially" is of a different scope than the phrase "consisting of," as suggested by Applicant's interpretation. The transitional phrase "consisting essentially of" limits the scope of a claim to the specified

materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). However, since the exact nature of the nucleotide sequences that would not materially affect the basic and novel characteristics of SEQ ID NO: 4 are not clearly defined in the specification as filed, it is unclear what other embodiments are encompassed by those claims that recite the phrase "consists essentially of the nucleotide sequence set forth in SEQ ID NO:4." Additionally, in regards to the claims of the issued patent, it is not incumbent upon the PTO to prosecute related applications in an identical fashion, since the facts in each application are considered independently.

Applicants have not provided a clear nexus between the use of the HYB 165 oligonucleotide, particularly in a mouse model, and the use of all oligonucleotides encompassed by the methods of the claimed invention, specifically in organisms other than the mouse. Applicant's arguments do not take the place of evidence. The instant claims remain rejected under 35 USC 112, first paragraph since the specification as filed does not provide sufficient guidance and/or instruction that would allow one of skill in the art to practice the full scope of the claimed invention without undue experimentation. This conclusion is based upon the known unpredictability regarding the delivery and behavior of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, the lack of guidance provided in the specification as filed in this regard, and the breadth of the claimed invention.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 8:30AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps, Ph.D.
Examiner
Art Unit 1635

*JLE*
May 28, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635